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PERIPHERAL AND CARDIAC FACTORS IN EXPERIMENTAL SEPTIC SHOCK

Lerner B. Hinshaw

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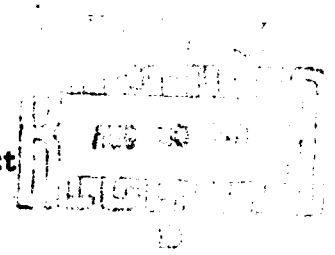

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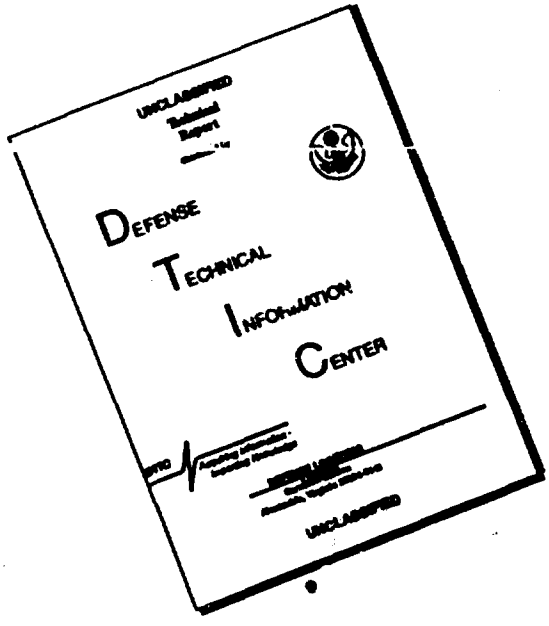

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13. ABSTRACT

Peripheral pooling mechanisms apparently predominate in the early phase of endotoxin shock in bringing about a decrease in cardiac output. Left ventricular function appears to be entirely normal and only a longer sustained period of hypotension would be expected to bring about impairment of myocardial performance. A variety of indirect mechanisms resulting from poor systemic hemodynamic status may ultimately contribute to myocardial failure in the later stages of shock.

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Introduction

The insidious and sometimes precipitous development of septic shock in man involves mechanisms not clearly understood. Cardiovascular changes have been reported to occur within seconds following an intravenous injection of endotoxin in dogs (5,7,19,22), and at variable times after injection of endotoxin in monkeys (8,10,13) or live E. coli organisms in the canine and primate species (3,11,14,15). Although the animal shock model has been studied extensively in recent years, the precise mechanisms involved in the early development of shock are not clearly understood. Recent emphasis has been focused on the causes of inadequate tissue perfusion in this form of shock. Of particular importance have been studies in which cardiac output decreased significantly in the early phase of shock. Several explanations have been proposed to account for the early decrease in flow and these will be the subject of this presentation.

Peripheral pooling mechanisms.

Venous return decreases in the mammalian species following administration of endotoxin (13,22) which may readily account for the reported decrease in cardiac output. Peripheral mechanisms resulting in the early sequestration of blood in various organs or anatomical regions have been described (4,6,9,12, 13,16,19,22) and seem to vary with the species (12). There is evidence for hepatosplanchnic pooling in the dog (6,9,19,22), extra-hepatosplanchnic pooling in both dog and monkey (4,12,13), and pulmonary pooling in the latter species (13). There is no evidence for early pooling in skin and muscle in any species (7,16). Early sequestration of perfusate in the monkey is primarily intravascular and is apparently quite generalized according to a recent study carried out in this laboratory (8,13). Trapping of blood in the subhuman primate appears to occur not only in the pulmonary bed, but in

the capacitance vessels of the systemic circulation and in dilated pre-capillary vessels (13).

Cardiac Mechanisms

Although the evidence is strong for a significant degree of peripheral pooling of blood in the endotoxin animal model, the possibility exists that cardiac mechanisms may also be elicited to effectively diminish cardiac output in the early phase of shock. Endotoxin could conceivably poison the heart directly, or indirectly bring into play detrimental circulating factors which of themselves might depress myocardial contractility. Evidence for heart failure in endotoxin shock in animals (1,21) and septic shock in man (2.20) has been published.

The concern of this report is focused on the role of the heart in the early phase of shock before long standing effects of poor perfusion have most probably damaged the myocardium. In the latter situation, all organs would eventually fail to function. However, the present discussion is focused on the earlier period of shock which might conceivably provide insight into the role of the heart. If the heart is found to fail early, that is, within 2-4 hours after endotoxin, cardiac failure could be established as a precipitating factor in the development of irreversible shock.

Research from this laboratory has failed to provide evidence for an early detrimental action of endotoxin on the myocardium (17,18), and even the effects of systemic hypotension and acidosis after endotoxin have provided no evidence for early heart failure. Death is seen to occur in animals receiving endotoxin, but a normal heart continually exchanging blood with the shocked animal performs normally (17,18). Three hours of systemic hypotension and depressed cardiac output after endotoxin fails to elicit myocardial damage, while left ventricular

end diastolic pressure, myocardial contractility, cardiac power (work/sec), dP/dT, O_2 uptake and CO_2 production are unchanged from control values 200 minutes after endotoxin injection (17). Cardiac performance is also found to be unimpaired after endotoxin in the presence of beta adrenergic blockade (18). Normal cardiac contractility is observed in the presence of acidosis, and myocardial O_2 uptake is found to be independent of pH values. Coronary blood flow is diminished in the hypotensive state but elevated markedly above control values when mean arterial pressure (afterload) is returned to the control (pre-shock) level. Oxygen delivery to the heart appears adequate since O_2 uptake is normal and coronary venous O_2 content is elevated above control values when afterload is restored to pre-shock levels.

These studies appear to clearly demonstrate that endotoxin exerts no early direct toxic action on the myocardium but that indirect factors most probably intervene during the intermediate or later stages of shock. The effects of prolonged systemic hypotension and progressive peripheral pooling would be expected to result in the eventual depression of cardiac function at later stages of shock on the basis of diminished coronary perfusion pressure and insufficient myocardial blood flow.

Summary

Peripheral pooling mechanisms apparently predominate in the early phase of endotoxin shock in bringing about a decrease in cardiac output. Left ventricular function appears to be entirely normal and only a longer sustained period of hypotension would be expected to bring about impairment of myocardial performance. A variety of indirect mechanisms resulting from poor systemic hemodynamic status may ultimately contribute to myocardial failure in the later stages of shock.

References

1. Alican, F., M. L. Dalton, and J. D. Hardy. Experimental endotoxin shock Am. J. Surg. 103:702-708, 1962.

2. Bell, H., and A. Thal. The peculiar hemodynamics of septic shock. Post Grad. Med. 48:106-114, 1970.

3. Guenter, C. A., V. Fiorica, and L. B. Hinshaw. Cardiorespiratory and metabolic responses to live E. coli and endotoxin in the monkey. J. Appl. Physiol. 26:780-786, 1969.

4. Hinshaw, L. B., R. P. Gilbert, H. Kuida, and M. B. Visscher. Peripheral resistance changes and blood pooling after endotoxin in eviscerated dogs. Am. J. Physiol. 195:631-634, 1958.

5. Hinshaw, L. B., J. A. Vick, M. M. Jordan, and L. E. Wittmers. Vascular changes associated with the development of irreversible endotoxin shock. Am. J. Physiol. 202:103-110, 1962.

6. Hinshaw, L. B., and D. L. Nelson. Venous response of intestine to endotoxin. Am. J. Physiol. 203:870-872, 1962.

7. Hinshaw, L. B., C. M. Brake, T. E. Emerson, Jr., M. M. Jordan, and F. D. Masucci. Participation of the sympathoadrenal system in endotoxin shock. Am. J. Physiol. 207:925-930, 1964.

8. Hinshaw, L. B., T. E. Emerson, Jr., and D. A. Reins. Cardiovascular responses of the primate in endotoxin shock. Am. J. Physiol. 210:335-340, 1966.

9. Hinshaw, L. B., D. A. Reins, and R. J. Hill. Response of isolated liver to endotoxin. Canad. J. Physiol. Pharm. 44:529-541, 1966.

10. Hinshaw, L. B., M. M. Jordan, and J. A. Vick. Histamine release and endotoxin shock in the primate. J. Clin. Invest. 40:1631-1637, 1967.

11. Hinshaw, L. B., L. A. Solomon, D. D. Holmes, and L. J. Greenfield. Comparison of canine responses to E. coli organisms and endotoxin. Surg. Gynec. Obstet. 127:981-988, 1968.

12. Hinshaw, L. B. Comparative effects of endotoxin on canine and primate intestine. J. Surg. Res. 8:535-538, 1968.

13. Hinshaw, L. B., L. L. Shanbour, L. J. Greenfield, and J. J. Coalson. Mechanism of decreased venous return in subhuman primate administered endotoxin. Arch. Surg. 100:600-606, 1970.

14. Hinshaw, L. B., M. C. Mathis, J. A. Nanaeto, and D. D. Holmes. Recovery patterns and lethal manifestations of live E. coli organism shock. J. Trauma 10:787-794, 1970.

15. Hinshaw, L. B. Physiological responses to infectious agents. Internat. Symposium, Resistance to Infectious Disease. Saskatoon Mod. Press. Saskatchewan, Saskatoon, Canada, pp. 85-91, 1970.

16. Hinshaw, L. B., and S. E. Owen. Correlation of pooling and resistance changes in the canine forelimb in septic shock. J. Appl. Physiol. 30: 331-337, 1971.

17. Hinshaw, L. B., L. T. Archer, L. J. Greenfield, and C. A. Guenter. Effects of endotoxin on myocardial hemodynamics, performance and metabolism. Am. J. Physiol. (in press).

18. Hinshaw, L. B., L. J. Greenfield, L. T. Archer, and C. A. Guenter. Effects of endotoxin on myocardial hemodynamics, performance and metabolism during beta adrenergic blockade. Proc. Soc. Exptl. Biol. Med. (in press).

19. MacLean, L. D., and M. H. Weil. Hypotension (shock) in dogs produced by Escherichia coli endotoxin. Circulation Res. 4:546-556, 1956.

20. Siegel, J. H., M. Greenspan, and L. R. M. Del Guercio. Abnormal vascular tone, defective oxygen transport and myocardial failure in human septic shock. Anns. Surg. 165:504-517, 1967.

21. Solis, R. T., and S. E. Downing. Effects of E. coli endotoxemia on ventricular performance. Am. J. Physiol. 211:307-313, 1966.

22. Weil, M. H., L. D. MacLean, M. B. Visscher, and W. W. Spink. Studies on the circulation changes in the dog produced by endotoxin from gram-negative micro-organisms. J. Clin. Invest. 35:1191-1198, 1965.